false membrane, much like a sheet of cellophane, had exfoliated, the baby's skin showed dryness, was cyanotic, and lacked the abundance of subcutaneous fat normally present. As the babe grew, the skin gave the appearance of the common type of ichthyosis.

❋

ERNEST K. STRATTON, M. D. (490 Post Street, San Francisco).—Through the courtesy of Doctor Seitz, I had the privilege of seeing the patient herein reported on two different occasions—first, while it was still in the hospital (aged four weeks), and again when it was nine months of age. When I first saw the patient, the skin on most of its body truly resembled that of a baked apple. With such a generalized involvement, the marked ectropion and the fixation of the skin on its hands and feet, I did not see how it could possibly survive; yet, a few months later, the child resembled a normal one, with the exception of the ordinary ichthyosis which Doctor Seitz has mentioned.

I think Doctor Seitz is to be congratulated on the skill and perseverance which he gave to this case. For without such intelligent handling the case report would have included, in all probability, the necropsy findings as well.

The biopsy taken at the age of nine months showed a moderate ichthyosis only. I would like to have seen a section of skin from the "collodion" areas taken earlier in the baby's life.

I agree with Doctor Seitz regarding the classification of this case. It is mixed, belonging partly in the second group, "Ichthyosis congenita larvata," and partly in the third group, "Ichthyosis congenita tarda."

❋

DONALD A. DALLAS, M. D. (490 Post Street, San Francisco).—Doctor Seitz has presented a report of a case very rare in medicine, and I think that he should be congratulated on his excellent work in keeping this unusual child alive and well.

This baby was delivered by low forceps after a normal pregnancy and labor. I was astounded at the appearance of this child on delivery. It was a deep purple in color, with the exception of a few areas over the body, the nose, the palms of the hands, and the soles of the feet, which were the color of ivory. The skin over most of the body appeared to be transparent, was smooth, and glistened in the light. It was not until the skin began to dry that it took on the characteristic wrinkled appearance. The child cried lustily immediately after birth, and its general condition seemed good. I thought, however, that it would surely die within a few days; but under Doctor Seitz's care it has thrived. I hope that the progress of this unusual child will be reported at future meetings of this section.

❋

DOCTOR SEITZ (Closing).—I wish to reaffirm my observation that no distinct epitrichial membrane was identified in the case reported here. While desquamation was more pronounced in earliest infancy, it continued abundantly during the whole first year, and I cannot convince myself that this persistent and universal shedding has been caused by a retention of the fetal epitrichial membrane.

AGRANULOCYTOSIS*

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DISCUSSION *by Olin H. Garrison, M.D., Oakland; Stacy R. Mettier, M.D., San Francisco; Fred H. Kruse, M.D., San Francisco.*

DURING the past few years, the condition commonly known as agranulocytosis has appeared with great frequency in the medical literature and before scientific gatherings. However, one has but to glance at the literature to be aware of the divergence of opinion and confusion of ideas which have been presented. It would seem worth while to review this information and to attempt to coördinate it.

The condition is generally regarded as a fulminating illness of unknown etiology, characterized by a marked reduction in the total number of white cells and by a great reduction in the percentage of granulocytes, unaccompanied by notable anemia, in which both hypoplastic and hyperplastic myeloid tissue have been described.[1]

NOMENCLATURE

Various authors have proposed different names for this same condition, on the basis of a correct descriptive nomenclature. The term "agranulocytosis" was applied to the condition by Schultz[2] in his original description. Friedmann[3] added the term "angina" because of the frequent occurrence of painful throat lesions. Baldridge and Needles[4] applied the term "idiopathic neutropenia." Schilling[5] suggested "malignant neutropenia." Other terms, such as agranulosis, granulocytopenia, and pernicious leukopenia, have been proposed. For the purposes of this paper, it makes little difference what term is used so long as we are certain that we are discussing the same condition.

HISTORY

Pepper,[6] in his history of malignant neutropenia, is of the opinion that the disease was described some fifty years ago in the laryngological texts under the heading of "putrid sore throat," or "gangrenous angina." He states that probably the first case reported in this country was that of Brown and Ophüls,[7] in 1902, as a fatal case of "acute primary infectious pharyngitis." However, it was not until Schultz[2] described his four cases, stating that he believed the disease represented a distinct clinical entity, that the condition was brought into sharp relief. Following the report of Lovett[8] in 1924, interest was stimulated in this country, and since then the literature has fast multiplied.

ETIOLOGY

Many authors have taken the stand that the disease is not a clinical entity but, rather, a syndrome common to many pathological conditions.[9,10,11] It is a known fact that a leukopenia and neutropenia, of severe grade, may occur secondary to aleukemic leukemia,[10] aplastic anemia,[10] sepsis,[9,12,13] arsenic poisoning,[14,15] benzene poisoning,[16] and following the administration of the arsphenamins.[17] However, numerous case reports have appeared where these factors are totally absent and, as pointed out by Jackson,[18] this fact should not militate against an entity any more than the fact that a pernicious anemia picture may occur with dibothyrocephalus infection, with carcinoma of the stomach and following gastric resection militates against pernicious anemia as an entity. Also, in the case of aleukemic leukemia, there is usually evidence of a disturbed erythropoietic and thromboplastic function, as well as myelopoietic, and the same is true of the arsenicals and benzene. So the blood picture itself is not that of a true granulopenia.

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Sepsis or infection as an etiologic agent has not been a universal finding in all cases, as pointed out. Also Jackson,[18] Roberts and Kracke,[19] have reported the typical picture preceding the onset of sepsis or an infection. Efforts to experimentally[20,21] produce the condition by means of an infective agent have failed to produce the typical picture. The frequent occurrence of a sepsis is probably best explained as an invasion of a relatively defenseless organism as a result of the granulopenia.

Pepper[22] has suggested the possibility of allergy as an etiologic agent. Schilling[5] produced a picture somewhat similar to agranulocytosis by means of anaphylactic shock. Bromberg and Murphy[23] and Kracke,[24] each have reported a case following prophylactic vaccination against typhoid. Jackson and associates[18] state they have seen cases develop following administration of sera and antitoxin. However, allergy has not been a universal finding, and would not seem to be a major etiologic factor.

The fact that there are instances of onset of the disease coincidental with menstruation, as reported by Thompson[25] and Jackson, et al.,[26] and the periodicity of attacks occurring at regular intervals in the case of Doan[27] and that of Rutledge, Hansen-Pruss and Thayer[28] have suggested the possible rôle of some endocrine disturbance. However, the menstrual relation in the case of Thompson and that of Jackson could be explained on the basis of chance occurrence alone, and the fact that the relationship is only an occasional finding would seem to minimize it as an etiologic factor. In Doan's case he states that there was no menstrual relationship with the attacks. There has been to date no majority of cases which have demonstrated an associated endocrine disturbance. Thus it would seem that the endocrine factor was not a consistent one.

With the announcement a year ago of Madison and Squier[29] that in fourteen consecutive cases of typical agranulocytosis, amidopyrene, either alone or in combination, had been ingested previously, and that in the six cases of patients who continued to take the drug the mortality was 100 per cent, whereas in the eight in which the drug was discontinued the mortality was but 15 per cent, served to focus attention upon the relationship of this drug to the syndrome. Also, the positive relationship seemed to be strengthened by the fact that in two of the cases following recovery a positive temporary granulopenia was produced by a single small dose of the drug. Following this announcement, there were additional reports by Rawls,[30] who also was able to produce a recurrence in one patient after administering 280 grains of the drug. Hoffman, Butt and Hickey,[31] Watkins,[32] Fitz-Hugh,[33] and Randall,[34] pointed out a similar relationship. However, Jackson,[35] in an analysis of twenty-seven cases in which he possessed complete data relative to medication, found that in only seven cases could the drug be regarded as responsible for the condition. Similarly Seeman,[36] in analyzing thirty-six cases, found that in but thirteen had amidopyrene been taken. Rawls states that in two hundred patients who had been taking amidopyrene regularly, two developed a granulopenia. Due to the fact that in the series of Madison and Squier[29] and Watkins,[32] barbiturates had been frequently taken in combination with amidopyrene, it was felt that perhaps the former possibly played a part. However, to date there have been no cases in which a barbiturate alone has been responsible. This fact would seem to exonerate the drug. In June, 1934, the Council on Pharmacy and Chemistry of the American Medical Association, after investigating this phase concluded: "As far as can be learned from the evidence at hand, there can be no question that amidopyrene is very important in the production of granulocytopenia. . . . In the second place, no definite case has been reported in which a barbiturate alone has been responsible. There is no doubt that many cases of granulocytopenia have occurred in which amidopyrene has never been taken." This evidence would seem to incriminate amidopyrene as a factor in producing granulocytopenia, but certainly proves that it is not the universal etiologic factor.

During the past year a similar relationship between dinitrophenol and the disease has been reported by Hoffman, Butt and Hickey,[37] Bohn,[38] Davidson and Shapiro,[39] Dameshek and Gargill,[40] and Silver.[41] This fact, therefore, should be regarded when administering the drug for therapeutic purposes.

Hart[42] and Zinninger[43] have reported the occurrence of a malignant neutropenia in two sisters. This fact has suggested the possible rôle of a familial tendency. However, this observation has not been constant and would seem not to be of importance.

When all factors have been considered, there is no doubt that certain chemicals and toxins can produce an agranulocytosis. There still remains a group of cases for which no etiologic agent has been demonstrated. That these may constitute an entity is possible, but as yet this is not proved.

PATHOLOGY

Studies on bone-marrow pathology have been confusing, as some[44,45,46,47,48] have reported "granulocytic aplasia," while others[18,49,50,51,52] have found a normal or increased myeloid activity. However, in the latter studies there is an absence of the mature granulocytes. Some have reported the presence of myelocytes, and others have found nothing beyond the development of so-called "stem" cells. Fitz-Hugh and Krumbhaar,[53] in a thorough study of three cases, had similar findings and postulated their theory of "maturation arrest." Custer,[52] after studying the bone marrow of eleven cases, had similar findings in nine, with a moderate hypoplasia in two, although the qualitative changes in these two were of the same nature; and he is inclined to agree with the theory of "maturation arrest." Jackson,[18] after examining the marrow of twenty-five fatal cases, found no evidence of a hypoplasia in those dying early in the course of the disease, while in those patients who survived the ravages of infection for a period

of eight to twenty days, the bone marrow was found to be relatively hypoplastic. These findings may serve to explain to some extent the heretofore apparently opposite findings by different writers. Jackson also found no granular cells developed beyond the "stem cell" stage. He also would agree with the theory of "maturation arrest" of Fitz-Hugh and Krumbhaar. It would seem that the majority are in agreement that the erythropoietic and thrombopoietic elements are undisturbed, and when changes are shown here it is probably secondary to the toxemia or sepsis which has complicated the picture.

Ulcerative and gangrenous lesions of the oral cavity, gastro-intestinal tract and vagina are frequently described as brawny and edematous indurations showing an absence of polymorphonuclear leukocytes. Certain minor changes of the liver, spleen and lymph nodes have been described, but are generally regarded as secondary to the toxemia or an accompanying sepsis and not part of the agranulocytosis. In the cases complicated by sepsis those lesions common to any sepsis are described.

CLINICAL PICTURE

The clinical picture in general may be said to be characterized by a rapid or sudden onset, marked prostration, fever, headache, malaise, chills, sore throat, ulcerating lesions of the oral cavity and gastro-intestinal tract, and by extreme leukopenia and neutropenia unaccompanied by notable anemia.

The condition occurs far more commonly in women. Hueper,[54] from the literature, found 77 per cent in females as against 23 per cent in males. In Lichtenstein's[55] series there were twenty-four females and three males, or 89 per cent females. In Jackson's[18] series of 103 cases, eighty-three were found to be females and twenty males.

The incidence of the disease is greater in mid-adult life. It is very unusual for it to occur under the age of ten. Dameshek and Ingall[49] collected eleven cases from the literature under the age of ten, and reported two additional cases, one aged two, and one a child of sixteen months. Both were preceded by purulent otitis media. In the Jackson[18] series, there were none under the age of ten years. Beck[1] states that practically all cases occur between forty-one and fifty-eight. The greatest incidence in Jackson's[18] series was in the fifties, 29 per cent occurring in this decade. In this review of the literature, computed from ninety-two collected cases[1, 23, 27, 29, 32, 49, 56, 57, 58, 59, 60, 61, 66] 35 per cent were found to have occurred in the fourth decade of life.

In malignant agranulocytosis, the picture is that of an acute fulminating illness. The white count is rarely 2,500 per cubic millimeter, and often 1,000 or less, frequently in the hundreds. Neutropenia is extreme, with frequently a total absence of neutrophils and often not over 5 per cent. In Jackson's[18] series of 103 cases, thirty, or 28 per cent, had counts less than 500; twenty-eight, or 27 per cent, between 500 and 1,000; thirty-eight, or 37 per cent, between 1,000 and 2,000; and only seven, or 7 per cent, between 2,000 and 3,000.

Most observers[18, 27, 45, 53, 61, 65] report the platelets normal and a practical absence of anemia. Occasionally an anemia occurs secondary to a sepsis or in the terminal state of the disease. As one would expect from these findings, there is also reported an absence of a hemorrhagic tendency. Contrary to this, Roberts and Kracke[56] and Aubertin and Levy[11] find a thrombopenia, and are of the opinion that bleeding is a common manifestation. That these opposite findings may be explained on the presence or absence of a complicating sepsis, or a difference in the stage of the disease at the time of observation, is probable.

Jaundice has been frequently observed by Schultz[65] and Pepper.[22] Kastlin[45] reported its presence in 17 of 32 cases; Lichtenstein[55] in 8 of 27 cases; Jackson[18] in 7 of 103 cases. Chalier[67] and Jackson[18] are of the opinion that the jaundice is the result of hemolysis from secondary bacterial invasion. Certainly there is nothing in the primary pathology to explain a jaundice.

The spleen is but rarely enlarged and a lymphadenitis, except regional from a local infection, is most unusual.

Gangrene and consequent sloughing may occur, and when it involves the gastro-intestinal tract it is particularly dangerous. When present in the throat, an accompanying edema may prove a grave menace and require tracheotomy to render breathing possible.

The fever presents nothing characteristic. As a general rule, it is 102 to 103 degrees, although it may go to 106 or 107 degrees. Occasionally only a very low-grade fever is present.

That less severe cases of granulopenia occur has been pointed out by Mettier and Olsan,[62] Roberts and Kracke,[63] and by Doan.[27] In this type the outstanding feature is that of fatigue, and the mortality generally is lower than in the malignant type.

Chronic forms have been reported by Fitz-Hugh and Comroe,[61] Doan,[27] Rosenthal,[64] and others. These have been followed for periods varying from a month to as long as six years in Rosenthal's two patients. The leukocyte count is usually not below 2,000, and with neutrophils generally about 20 per cent, except in the terminal state, when the count may be as low as 500 and neutrophils absent. In Fitz-Hugh's[61] report of eighteen cases, five were of the chronic type, four of which died.

Recurrence following recovery is not uncommon. Harkins,[57] in 1932, collected thirty-six cases exhibiting recurrences, with intervals ranging from three months to two years. He states the mortality rate in recurrent cases is high, reporting[68] four patients, two of whom were dead at the end of two years. Beck,[1] Foran,[60] Heck,[69] and Zinninger,[43] each report a case. All but one of these patients were living at the end of periods varying from six months to a year and a half. Roberts and Kracke[56] report three patients, all of whom died. Fitz-Hugh reported two patients who were alive at the end of two and one-half years. This is a mortality of 50 per cent for the latter nine.

TREATMENT

The treatment has consisted of various and sundry measures, the most of which have been on an empirical basis. Single recoveries have been reported from such measures as quinin [70] and calcium gluconate.[71] A splenectomy [50] was performed in one case without benefit.

Nonspecific therapy in the form of parenteral foreign protein and intramuscular turpentine has been reported with recoveries. Roberts and Kracke [56] have adopted the use of intramuscular injections of turpentine on the basis that sepsis is desirable in promoting a leukocytosis. However, this reasoning would seem to be unsound, since in the experience of the majority sepsis has been believed to be a serious complicating factor. Dameshek [49] and Brooks [72] have reported recoveries following the use of intravenous nonspecific protein. That the leukocytic properties of protein therapy is chemotactic, and not maturative, would seem to lend no theoretical grounds for its use. Also it should be remembered that cases of agranulocytosis have been reported, following administration of foreign protein.[18, 23, 24] The consensus of opinion would seem to be that this form of therapy is without value.

Transfusions have been used by many, and recoveries have been reported. However, conclusions are difficult, as many other therapeutic procedures have generally been used on the same patients. In Harkins' [68] series, nine patients who were treated by transfusion were reported, with a mortality of 55 per cent. However, he concluded that the treatment was of little value. Beck [1] also reports a recovery following transfusion, but, like Harkins, concluded the treatment was of little value. Many others have reported recoveries following transfusion, but in combination with other procedures.

Fisher [73] and Harkins [68] each report a recovery following immunotransfusion. It would seem rather heroic to bleed a donor of known previous bone-marrow dyscrasia, and further there is no evidence that the blood of recovered patients contains immune bodies.

Sabin has shown that transfusion temporarily lowers the rate of erythropoiesis and perhaps granulopoiesis. This fact would seem to be borne out by the experience of Conner,[74] and Jackson,[18] who have reported an actual fall in leukocytes following the procedure.

Although the urge is strong to give blood in this state of leukocytic depletion, there seems to be no logical foundation for its use.

Liver extract is advocated by Foran on the basis of the findings of Murphy, Connery and Goldwater, and Conner, who observed a leukopoiesis in the treatment of pernicious anemia with parenteral liver extract. He treated five patients, with recovery in four, one of whom had several recurrences. Harkins [57] treated two individuals with liver extract, with recovery in one instance. Coggeshall [76] and Silver [41] each treated one case with failure. Jackson's [18] four patients were given liver as well as pentnucleotide, but all of these died. Few have had experience with this form of therapy, and as yet an insufficient number of patients have been reported to allow conclusions other than to say a few have been successfully treated. No contraindications to this form of therapy have been brought to light.

The use of x-ray over the long bones was suggested by Friedemann [77] in 1927. Some three years later Friedmann and Elkeles [78] reported their results on a series of twenty, with a mortality of 47 per cent. These were apparently true agranulocytics. However, as pointed out by Jackson [18] the entire series consisted of forty-three cases, of which twenty-three were excluded because of death within thirty-six hours, or the presence of sepsis or pneumonia. In the entire series the mortality was 82 per cent. Taussig and Schnoebelen [79] treated four cases, with a mortality of 50 per cent. In a résumé of the literature of all cases treated by this means, they found a mortality of 53 per cent. Lichtenstein [55] treated twenty cases, immediate improvement following in seven. A year later all were dead except two, a mortality rate of 90 per cent. Beck [1] reports three cases, with recovery of one. Harkins [57] treated two cases, both resulting in death.

Doan [80] studied the effect of varying small doses of x-ray on myelopoiesis in pigeons. He found no stimulating dose which did not show some prior evidence of myelocytic destruction. As reported by Fiersinger, x-ray is also capable of producing the picture of agranulocytosis—a fact which should not be forgotten.

It would seem from these facts that there is no evidence to recommend x-ray as a therapeutic weapon. It is possible that it may have a deleterious effect.

The arsphenamins were formerly used to some extent earlier in the treatment of the disease. This was on the basis of the observation that Vincent's organisms, frequently found in the throat lesions, were presumed to be etiologic factors. We now recognize them as secondary invaders. Following the report of Farley [17] and the experience of others, which unquestionably demonstrates its depression of the bone marrow in certain instances, the employment of this agent would seem to be irrational.

Adenin sulphate was advocated by Reznikoff [81] on the basis of its known ability to produce a leukocytosis. In 1933 he reported fifteen cases [82] of apparently true agranulocytosis, with a mortality of 26 per cent. His conclusions were conservatively optimistic.

Jackson, [75] having demonstrated the presence of pentnucleotide in the normal human blood, and Doan [83] et al. having demonstrated the ability of nucleic acid and its derivatives to produce a leukocytosis, the former applied these facts therapeutically, and in 1931 [75] reported twenty-six cases treated with pentnucleotide, with fourteen recoveries. Recently [18] he has reported on a series of 103 cases, including the original twenty-six, with a mortality of 33 per cent, all patients having been followed to the date of publication. So far as I have been able to ascertain, this is the largest series in which any one therapeutic meas-

ure has been employed under controlled conditions and certainly is, by far, the lowest mortality rate reported from any therapeutic procedure.

Baldridge,[50] Doan,[80] Mettier,[62] Bohn,[38] and others have used pentnucleotide with success.

Fitz-Hugh and Comroe,[61] Zinninger,[48] and Harkins[57] report less success. However, their series are small, and there is some question as to whether theirs were all true agranulocytosis.

Jackson[18] advises the administration of 10 cubic centimeters (pentnucleotide, N. N. R.) intramuscularly twice, or preferably three times, daily until the white count has risen and young neutrophiles have appeared. Thereafter 10 cubic centimeters daily should be administered until the white count has remained normal for several days.

The response, when it occurs, takes place about the fourth or fifth day (Doan[80] and Jackson[18]), and is manifest first by the appearance of myelocytes in the blood stream, at times reaching a level as high as 20 per cent. Shortly thereafter mature neutrophiles appear in increasing numbers until a normal white count is reached.

Surgical intervention has been considered by some to be positively contraindicated (Beck[1] and Roberts and Kracke[56]). Others have reported rapid recoveries following opening of abscesses, thoracotomy, amputation of gangrenous extremities, and drainage of purulent adenitis (Thompson and Jackson[18]). Jackson[18] attributes a death to lack of surgical intervention in a patient who had developed a normal blood picture. That an elective procedure should be avoided is evident.

The oral and pharyngeal lesions do best when treated by simple hygienic measures, and all procedures causing trauma to these areas are objectionable.

Based on the known leukotoxic effect of the benzene ring, all drugs containing such a structure should be avoided.

It is hardly necessary to state that adequate nursing, maintenance of nutrition and fluid balance are of the utmost importance.

SUMMARY

That certain chemicals and toxins are capable of producing an agranulocytosis is evident. However, there still remain a group of patients in whom no etiologic agent has been demonstrated. That these may represent an entity is possible.

The pathology of the bone marrow has been reported by some as a hypoplasia of the myeloid tissues. Those who have made a careful study of any considerable group report in the majority of instances a hyperplastic or normal amount of myeloid tissue, but with an absence of forms beyond the stem or "blast" stage of maturation. On the latter findings the theory of "maturation arrest" has been postulated. Other pathologic findings are frequently present, but are considered secondary to toxemia or a complicating sepsis.

The usual clinical picture has been briefly given. It is pointed out that the disease is much more common in women, and occurs most frequently in mid-adult life. The blood picture consists of marked leukopenia and neutropenia, and usually an absence of anemia or thrombopenia, although a minority have reported the presence of anemia and a reduction in platelets. There is usually an absence of any hemorrhagic tendency. Splenomegalia is usually absent and never extreme; and a lymphadenitis, except regional, is most unusual. Ulcerative and gangrenous lesions of the oral and gastro-intestinal tracts are common. Jaundice has been observed not infrequently. Mention is made of a less severe and fulminating type as well as a chronic form. Recurrences following recovery are not uncommon.

The therapeutic measures most frequently employed, consisting of nonspecific therapy, transfusion, liver extract, x-ray, arsphenamin, adenin, and pentnucleotide, have been discussed. It is obvious that there is no specific therapy, but of the agents mentioned, pentnucleotide would seem to offer the best results.

The wisdom of surgical intervention has been briefly discussed. It would seem logical and correct that any complication, with positive indications for necessary surgical interference, should be so treated. Mention is made of a patient who, in the opinion of the author, died because of lack of surgical intervention.

Proper nursing care, maintenance of sufficient fluid intake and an ample caloric intake are factors of the utmost importance.

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DISCUSSION

OLIN H. GARRISON, M. D. (411 Thirtieth Street, Oakland).—Doctor Railsback has given us an excellent review of the literature, and has emphasized the important points relating to this interesting disease.

It seems to me that the majority of evidence forces one to the conclusion that agranulocytic angina is a definite disease entity. Certainly a pernicious leukopenia is as logical as a pernicious anemia.

It is fairly well established that this disease may be caused by an idiosyncrasy to certain drugs, especially those containing the benzene ring. It is equally certain, however, that the disease may occur without the ingestion of these drugs. No one, in my series of cases, gave a history of taking drugs.

I have never been impressed with the value of whole-blood transfusions in these cases. I have repeatedly transfused my patients, only to find, on taking a blood count one or two hours later, that there was no change whatsoever in the leukocyte count. Apparently, the injection of pentnucleotid has given the largest number of favorable results. There is one objection, however, to this drug, and that is, that there is a latent period of four or five days before improvement is noted. When the patients are as desperately sick as they usually are, it is very trying to wait for this period of time.

I have recently used intramuscular injections of concentrated liver extract, and felt that it was of definite benefit. Certainly there is no contraindication, and many observers report a leukopoiesis in the treatment of pernicious anemia.

But in a certain number of patients the disease is so fulminating that I do not believe they can be saved with any form of therapy known at the present time.

STACY R. METTIER, M. D. (University of California Medical School, San Francisco).—Unfortunately, "agranulocytosis" is a term that has come into rather wide usage. It is a poor one to use, because it fails to describe definitely a disease process. Actually, agranulocytosis means a leukocytosis of agranular cells. Perhaps the words "neutropenia" or "granulocytopenia" would be more descriptive of the reduced neutrophilic elements in the circulating blood.

Neutropenia may be associated with many conditions, and may vary in frequency from 11.67 per cent of University of California Hospital entries over a ten-year period, as reported by this author, to 23 per cent, as recorded by Roberts and Kracke from their office practice. This large group of cases is comprised mostly of various infections, neoplasms, lymphomas, or results from the prolonged use of x-ray or radium and drugs that destroy blood-forming tissue or inhibit leukopoiesis. From these may be separated a small group of cases characterized by severe neutropenia, lymphopenia and associated infection of the mucosa of the oral cavity, gastro-intestinal tract or vagina. It is in this latter group that amidopyrin seems implicated. Here leukopoiesis in general is depressed, and granulopoiesis in particular. So far as we have learned at the present time, failure of complete maturation of leukocytes occurs, but in contradistinction to leukemia or pernicious anemia the bone marrow remains relatively hypoplastic rather than becoming hyperplastic. In a restricted sense, the term "agranulocytosis," as described by Schultz, or malignant leukopenia, may best designate this condition until we learn more about its exact identity.

It is only within recent years that leukopenia has attracted sufficient interest to warrant a classification. In our textbooks of medicine of only a few years ago, little mention was made of this subject. Perhaps we would have a better understanding of the problem of classifying leukopenia by designating it as benign or malignant leukopenia of known or unknown etiology or, even better, by speaking of depressed function of leukopoiesis, whatever may be the cause.

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FRED H. KRUSE, M. D. (384 Post Street, San Francisco).—Doctor Railsback has given an interesting review of this subject of agranulocytosis, emphasizing the characteristic findings in the blood of neutropenia, rather than any form of leukopenia; a septic type of fever, and a local focus of infection either in the throat, skin, or internal viscera. Such a summary is invaluable to the general medical man, particularly on such a subject as agranulocytosis or malignant neutropenia, in reference to which the literary contributions in the last few years have been continuous, voluminous and conflicting, both as to etiology and treatment.

Certainly every suggestion in reference to the disease grips the attention of the general profession; because the throat specialist, the surgeon, the practitioner, the internist, the hematologist, and the pathologist yearly search frantically for new aids as a sorely stricken patient spurs their endeavors, which generally culminate in a sense of futility and helplessness.

I can well recall my earliest experiences with the disease back in 1918 and 1919. The clinical picture then recognized included gangrenous throat, septic fever, and a low white count in a practically moribund patient. Throat smears disclosed Vincent's organisms (spirochetes and fusiform bacilli), and for that reason neosalvarsan was given intravenously, supplemented later by blood transfusions, and, too frequently, by extraction of teeth if the gangrenous lesion extended to the gums.

As my experience has widened, it has seemed evident to me that in this clinical syndrome we encounter three types of cases, namely, (1) relatively mild cases in patients who, though very acutely sick, get well shortly no matter what the therapy is; (2) patients with a more prolonged illness, not so acutely sick who, even while in the hospital, have remissions and relapses which may continue over a period of years; and (3) those fulminating septic cases, with a rapid downward course from the start and no sign of a remission no matter what the therapy is.

Whether No. 1 later on shades insidiously into No. 2, and whether No. 3 is only the terminal relapse of the No. 2 stage, which had escaped previous recognition is, of course, possible. At any rate, the success of our therapy may depend pretty much upon the stage at which we happen to encounter our patient.

I also want to emphasize the three most common and characteristic local types of lesions which I have encountered in these agranulocytic cases. They are the gangrenous throat or gangrenous gums, one often shading into the other; scattered lesions of the skin, vesicular, bullous or furuncular in appearance, and finally brawny indurations about the rectum with terminal gangrenous sloughing. The surgeon must be exceedingly cautious in attacking any of these lesions. And while on this subject, it has appeared illogical to me to attempt to bring out a granulocytic response by producing a sterile abscess, such as by turpentine.

In treatment, certainly the pentnucleotids must be used, but so far they have proved only a help, not a cure. The dangers of transfusion in depressing the neutrophilic response must always be considered. I have thought small transfusions at times helpful. I must admit that I have been more intrigued by the possibilities of parenteral liver therapy than most of the other procedures, and consistently use it in all such cases.

This has been not only on account of the work of Murphy et al., but because of the favorable response of casual cases of leukopenia, with or without neutropenia, which I have encountered in practice and been unable to explain adequately. A number of such cases with low white counts, asthenia, cold extremities, etc., definitely improve on parenteral liver therapy. Are they latent cases of agranulocytosis?

THE IMPORTANCE OF LESIONS OF THE INTERVERTEBRAL DISCS IN RELATION TO TRAUMA*

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LESIONS of the intervertebral discs have recently attracted considerable interest. From the standpoint of industrial medicine, such lesions have importance because they are frequently observed. When there has been a history of trauma in which the spine might have been injured, and these lesions are seen on an x-ray film, the question at once arises as to whether they were preexistent or actually the direct result of trauma.

The work of Schmorl,[1] who since 1925 has examined at autopsy almost ten thousand spines, has given the greatest impetus to interest in lesions of the intervertebral discs; but the subject is by no means a new one, for in 1858 Luschka[2] wrote what is probably the best account of spinal anatomy to be found in the literature, in which he described certain pathologic changes, including posterior prolapse of the intervertebral disc.

ANATOMY

The central portion of the end surface of an adult vertebral body shows in a position corresponding to the nucleus pulposus, a disc of what appears to be compact bone. On closer examination, however, this disc is seen to be perforated by numerous very fine holes which represent the tiny foramina through which the nutrient vessels pass. It can easily be understood how, if the thin disc of cartilage which covers these tiny holes and constitutes the boundary between the bone and the nucleus pulposus were to fail, this perforated bone would not prevent the invasion of prolapsing nuclear substance in the same way which could be expected if the bone had a true cortex, such as is present in other articulating surfaces.

The intervertebral disc itself can be considered as being composed of three parts: the cartilage plates enclosing it above and below, the nucleus pulposus, and the annulus lamellosus.

The articular cartilages are two thin plates of ordinary hyaline cartilage, placed between the bony surface and the fibrous disc. Laterally, these plates disappear into the fibers of the discs. They are present, therefore, only over the porous central portion of the vertebral bodies.

The intervertebral disc proper consists of an annulus lamellosus—a fibrocartilaginous ring—which surrounds a central collection of gelatinous substance, the nucleus pulposus. The nucleus pulposus is of almost fluid consistency, but it is exceedingly firm and elastic. Judging by its behavior

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